

From the University Clinic for Rheumatic Diseases and Institute and
Policlinic for Physical Therapy
(Director: Prof. Dr. A. Böni)

Thesis prepared under the guidance of Dr. med. M. Rizzi

Agglutination of hemolytic Streptococci
in Gold Therapy of primary chronic Poly-
arthritis (Rheumatoid arthritis)

INAUGURAL DISSERTATION

for the degree of Doctor of Medicine from the Medical Faculty
of the University of Zurich

Presented by
JOSEPH MORTON LANGNER
of New York, USA

Accepted on the Proposal of Prof. Dr. A. Böni

Zürich 1954
Buchdruckerei Fluntern
Plattenstrasse 27

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INTRODUCTION

It has been a matter of discussion since the introduction of gold therapy in the treatment of primary chronic (rheumatoid) arthritis as to a method for evaluating its therapeutic efficiency. Coupled with this problem has been the lack of conclusive evidence as to a specific etiology of the said primary chronic polyarthritis.

It was shown by Lande (1927) and then by Forestier (1929) that, by use of gold salts, a definite improvement could be expected in a large percentage of cases of p. c. polyarthritis. Feldt and Beckstroem (1938) were able to demonstrate an improvement in 79% of their 750 cases. These results were found to be even higher (90%) in a later statistical evaluation. Cecil, Kammerer and DePrunde (1942) reported remission of symptoms in 39% of their 235 cases treated with gold salts. Fischer (1951) was able to show a marked improvement in one third of the 90 patients receiving therapy early in the disease. Therapeutic results were good and most marked in the 78% receiving therapy early in the disease. Rizzi (1953) also was able to show an improvement in 92,5% of his cases of rheumatoid arthritis. He, as well as Fischer, obtained particularly good results when the medicinal therapy was combined with physical therapeutic procedures.

One of the great barriers to the universal introduction of gold therapy has been the fear of reported toxic, even lethal, side effects occurring in a course of therapy with gold preparations. This fear has been allayed to a degree with the development of the newer colloidal gold preparations. However, this fear has led many to adopt a policy of resorting to gold therapy as a last resort. Adams and Cecil (1950) have shown an increased and accelerated remission of symptoms of rheumatoid arthritis if therapy was begun within

the first year of disease. This was corroborated by the later work of Eglius, Hävermark and Nystrom (1952).

In a study of 56 cases Svanburg (1950), by using an intracutaneous injection of aurothion (Astra) in dilutions of 1:1, 1:3, 1:5, 1:10 respectively, was able to demonstrate that increased reaction was followed by complications in 19 out of 20 cases. Decreased reaction was shown in 20 cases, of which only one case showed a complication. In 16 cases showing no change, 7 developed complications 9 none. In a follow-up study of 187 cases (1952) he could demonstrate complications in 73,2% of patients undergoing gold therapy, of these 64,5% showed an increased reaction during repeated tests, while in those showing a decreased reaction, only 12% developed complications. This change of degree of reaction occurred in immediate association with, or shortly following the first appearance of a complication. By using proper care, the danger of complications due to toxic effects of gold can be reduced to a minimum. Rizzi regards the complications as the result of a hyperergic reaction to gold as well as one of toxic nature.

It seems, however, for the present that gold therapy can be carried out only where the patient is under strict supervision such as in a clinic or clinical outpatients department.

As to the mode of action of gold salts, Feldt (1938) was of the opinion that gold worked both on the causative agent as well as on the patient by increasing the affinity of the disease agent to the gold, which was harmful to it, and by simultaneously increasing the metabolic activity of the host. This was derived from their work with spirochete infections in mice. This largely agreed with results derived by Jansco and Domayk. In 1939 Feldt and Beckstroem further clarified their views by concluding that gold acts by increasing local inflammatory reaction where the pathological processes are taking place, as well as by bringing about a histiocytic reaction in the reticulo-endothelial system. Dawson and Hobby (1950) showed that gold sodium-thiomalate has a bacteriostatic effect on *Streptococcus hemolyticus* in dilutions of 1:10 000. Hartung and Cotter (1941) further demonstrated that injections of gold salts were followed by a marked increase in bacteriostatic power of patient's serum against hemolytic streptococci in direct proportion to the amount of gold injected. Fischer (1951) was of the opinion

that gold acts as a bactericide and as a reticulo-endotheliotropic agent. In addition it has catalytic action on the patients metabolic processes.

Colloidal gold preparations have especially been found deposited in the liver, spleen, skin and kidney with the highest concentration in liver and plasma. This concentration is not significantly higher in the synovial fluid than in the plasma.

By use of radioactive gold preparations, Ely (1940) could demonstrate the presence of gold throughout all tissues, with the highest amount in the kidney and portions of the intestinal tract. He believes these to be the main avenues of excretion.

As to hemolytic streptococci being an etiologic agent in rheumatoid arthritis, Dawson, Olmstead, and Boots (1932) were able to show that the serum of rheumatoid arthritis patients agglutinated those strains of various hemolytic streptococci which did not agglutinate spontaneously. This they believed was an unspecific reaction. Cecil, Nicholls, and Stainsby (1931) had shown in previous experiments a positive agglutination with hemolytic streptococci but believed the reaction to be specific in respect to one strain.

Kalbak (1946) obtained positive agglutination in 76% of his cases with rheumatoid arthritis, as compared with 10% positive agglutination in patients with rheumatic fever, and a positive agglutination of 1,5% in control groups. In 1947 he obtained a positive agglutination to hemolytic streptococci in 80% of his rheumatic arthritis patients and very few positive agglutinations in a control group of 900. His work pointed in the direction of an unknown surface antigen being responsible for the reaction. This antigen is found only in the chronic cases. On the other hand Willis (1946) believed this reaction to be highly unspecific.

Thulin (1948) working with autoclaved (0) antigens found a positive agglutination to hemolytic streptococci in 92% of his cases with 60% having an agglutination value of 1:160 or more. He further demonstrated by antigen absorption procedures with acute or chronic polyarthritis, that this agglutination differed from that produced by living cultures.

Winblad and Edström (1948) were able to show an agglutination in 68% of 206 patients with rheumatoid arthritis, the titre ranging from 1:20—1:600. They concluded that the rise of the

titre could not be attributed to a non specific cause, such as protein fraction unbalance, but that in rheumatoid arthritis anti-body production increases with the increasing intensity of the disease.

Böni and Winblad (1948) were able to demonstrate a positive correlation between the erythrocyte sedimentation rate and the agglutination in rheumatoid arthritis patients. This correlation between agglutination and erythrocyte sedimentation rate was not noted in cases of tuberculosis.

Having established the presence of a relatively high and constant positive agglutination in the serum of patients with rheumatoid arthritis to hemolytic streptococci, and therefore an indication to the value of the streptococcal agglutination as a diagnostic aid, we are now in a position to determine what effect if any a course of gold therapy would have on the agglutination values of patients with rheumatoid (primary chronic) arthritis.

TECHNIQUE

A. L-agglutination

We adapted Kalbak's method which is as follows:

Group A streptococci are used. In this culture medium a diffuse growth takes place.

To 750 grams minced beef add 1,5 liters of tap water. Leave overnight in refrigerator (4 degrees C). Then boil for 15 minutes, filter through filter paper, adjust pH to 8,0 by adding 5N NaOH. Boil again for 30 min. To 500 ml of this extract add 5 grams peptone (Bacto-or Orthonapeptone) and 2,5 gram NaCl. Boil. Adjust pH to 8,0 by adding 5N NaOH. Filter into sterile flask, autoclave for 20 minutes at 120 degrees C. After autoclaving pH must be about 7,6—7,8.

Thus, a broth results which is rather poor due to the lack of glucose. The optimal growth time is more than 10 hours and less than 15 hours. This results in a culture which has optimal antigenic properties. The living culture is used as antigen and added directly to the serum dilutions.

The patient serum is diluted with 0,3% NaCl to 1:10—1:20 up to 1:1280. The same amount of living culture is added to each of the 8 tubes so that the final dilutions are 1:20—1:2560. After careful shaking, the tubes are left for 2 hours in a water bath at 52 degrees Centigrade. They are then left overnight in the refrigerator and read the next day. Readings are macroscopic, in degrees, used by Kalback as follows:

Deg. 0: No agglutination. Diffuse rising of sediment when flask is shaken gently.

Deg. 1: Sediment shakes up in small clumps. Liquid turbid, signifying partial agglutination.

Deg. 2: Sediment shakes up in small-medium size clumps. Fluid clear.

Deg. 3: Sediment shakes up in coarse clumps. Fluid clear.

Deg. 4: Large coherent disks. Fluid clear.

Negative reactions are all those in which the agglutination in the first tube is 0 or 1, regardless of degree in next tubes.

B. Gold Therapy

As carried out in the Institute for Phys. Therapy Zürich, the usual gold course lasts from 4 to 5 months during which 1 to 1,5 grams « Fosfocrisolo » (containing 21% gold) is given. During the course of treatment all laboratory controls (complete blood chemistry) are done weekly as well as careful checks on the general and nutritional condition of the patient. The schedule of administration for the gold compound used in this paper is as follows:

1. Week	$2 \times 0,001$ g. (every 3rd day)
2. Week	$2 \times 0,005$ g.
3. Week	$2 \times 0,01$ g.
4. Week	$2 \times 0,25$ g.
5. Week	$2 \times 0,05$ g.
6. Week	$2 \times 0,1$ g.

In extraordinary cases a dose of 0,2 g. is given.

PATIENT DATA

The data deals with the agglutination of the serum of 27 patient who have received gold therapy in varying amounts up to 2.587 grams Fosfocrisolo. As minimum data for agglutination scales, only those cases with 2 or more agglutination values have been taken. This method was used so as to record any changes in the agglutination values during therapy. Both clinical and polyclinical patients are included. For convenience the patients have been arbitrarily divided into groups as follows:

1. Those receiving less than 1 gram of Fosfocrisolo.
2. Those receiving 1 gram of Fosfocrisolo, or more.
3. Those showing 1 or more readings of 0 agglutination and their course (increase, decrease, or no change).

MANIFEST AGGLUTINATION

In our 27 patients we were able to establish that 18 (66,6%) showed a positive agglutination sometime during the course of treatment.

1. Course of Agglutination in those Patients Receiving Less than 1,0 grams Fosfocrisolo.

It is apparent from figure 1 that in the 9 cases receiving a total course of less than 1 gram that there is little or no correlation between the dosage given and the effect on the agglutination values. In the 9 cases the agglutination showed a decreased value in 1, an increased value in 1, and no effect on the 7 remaining. It should be pointed out, however, that although these patients showed a subjective improvement, the dosages given were not of such magnitude as to be completely indicative of the effect of gold on the titre of agglutination. They were included, however, to show what differences, if any, there are on the serum agglutinations of patients receiving a full or incomplete course of gold therapy.

(Fig. 1. Total Dosage Fosfocrisolo and Agglutination in 9 cases of Rheumatoid Arthritis Receiving Less Than 1.0 Grams).

2. Course of Agglutination in those Patients Receiving More than 1,0 grams Fosfocrisolo.

Here too it is apparent (see figure 2) that there is no correlation between gold dosage and agglutination even in a group of rheumatoid arthritis patients receiving relatively high quantities of gold. However, it is of interest to note that in 1 case, receiving a second course of therapy (10,10a), that though the first course, after an original decrease of agglutination value, was followed by a return to the original agglutination value; a second course was followed by a permanent drop of the agglutination value from 1:160 to 0. The results may be summarized as follows in that of the 18 patients, 6 showed decreased agglutination, 5 showed increased agglutination and 7 showed no change.

(Fig. 2. Total Dosage Fosfocrisolo and Agglutination Value in 18 Cases (1 second course) Of Rheumatoid Arthritis Receiving 1 or More Grams).

3. Of all the cases in our statistics (see Table 1) 18 (66,6%) showed one or more agglutination values of 0. Of these cases 10 (56%) showed no agglutination during the whole course of therapy. Of the remainder, 22% showed an increase from 0 to a positive reading with an equal percentage showing a decrease from a positive agglutination to 0. There were no decreases from positive to negative values in the group receiving less than 1,0 grams Fosfocrisolo while in the same group 20% increased from 0 to a positive value. In the group receiving 1,0 or more grams on the other hand, 30% showed an agglutination decrease to 0 as opposed to 23% showing an increase in agglutination from 0 to a positive value. Although the differences recorded in the two groups is by no means decisive, there is nevertheless an indication that with higher dosages a greater effect may be had on the agglutination values.

(Table 1. Those cases showing a 0 agglutination in course of therapy).

SUMMARY

In a group of 27 rheumatoid arthritis patients 18 (66,6%) showed, in a course of gold therapy, a positive agglutination value of 1:40 or more. Of these 52% showed no change in agglutination during the course, while 25,8% showed a decreased agglutination and 22,2% showed an increased agglutination.

It was further noted that of the 27 cases, 18 showed at least one negative agglutination value. 56% of these cases were those showing no agglutination throughout therapy. Of the remainder 22% showed a decrease from a positive to 0 value and 22% an increase from 0 to a positive value. It should be noted, however, that although there were no decreases in the below 1.0 gram Fosfocrisolo group, 30,7% of the patients in the 1 gram or more group showed a decreased agglutination value as opposed to an increased value in 23% of the same group.

It was not possible therefore to demonstrate a clear relationship between the amount of gold given in a course and an effect on the agglutination value, as manifested by an increase or decrease in said agglutination value. It is therefore impossible, on the bases of our results, to use the agglutination values of the sera of rheumatoid arthritis patients as a basis for judging the therapeutic efficiency of a course of gold therapy.

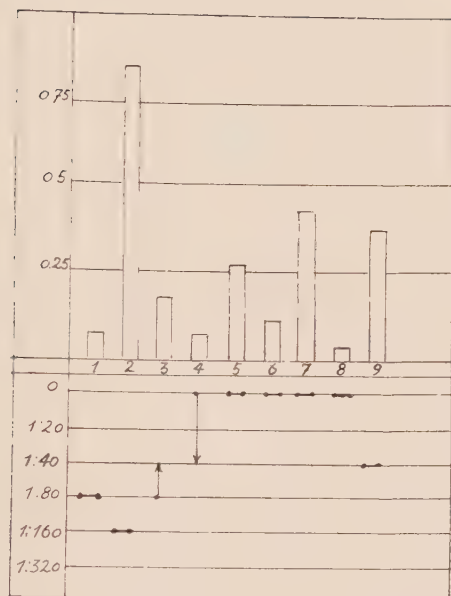


Figure 1:
Total Fosfocrisolo Dosage and Agglutinations in 9 Cases
of Rheumatoid Arthritis Receiving Less Than 1.0 Grams

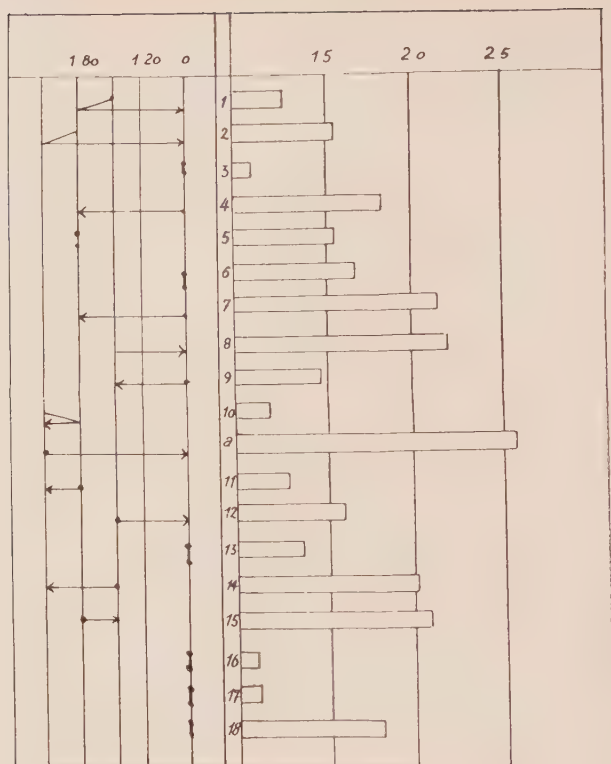


Figure 2:

Total Fosfocrisolo Dosage and Agglutination in 18 Cases of Rheumatoid Arthritis (one second course included)

Table 1

	less than 1.0 g	more than 1.0 g	total cases	percent
Cases w. no Aggl.	4	6	10	56%
Cases w. incr. Aggl.	1	0	4	22%
Cases w. decr. Aggl.	0	4	4	22%

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CURRICULUM VITAE

I was born in New York City on the seventh day of December nineteen hundred twenty-four. I attended elementary and high school in the State of New York. After completing high school I entered college. During my first year at college I enlisted in the reserve of the Army of The United States. I was soon called to active duty and served for a period of three years in the U.S. and Europe. After leaving military service I matriculated at New York University and received my A. B. degree in June 1948. I then matriculated at the University of Zürich, Faculty of Medicine, where I passed my second propaedeutische examination in 1950 and my Fachexamination for Ausländer in December 1953.

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